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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/051,843	01/17/2002	Kathleen H. Young	AHP 98133 P1	3063

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EXAMINER	
MURPHY, JOSEPH F	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/051,843	YOUNG ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6/17/2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45-51* is/are pending in the application.

4a) Of the above claim(s) *51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01172002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the species Kvβ1, and Kv1.1, in the reply filed 6/17/2004 is acknowledged. The traversal is on the ground(s) that Applicant are allowed to claim a reasonable number of sequences, up to 10, in a single application without restriction. This is not found persuasive because the inventions are distinct as noted in the last Office Action, as shown by the distinctness described therein. Applicant's attention is directed to MPEP 806.05. Furthermore, any search of the prior art in regard to the elected species will not reveal whether any prior art exists as to the other Groups, since a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112 first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of evaluating a compound for the ability to inhibit binding of an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins

are Kv1.1 and Kvβ1, does not reasonably provide enablement for a method of evaluating a compound for the ability to inhibit binding of an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1 wherein the proteins are biologically active fragments of the proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue.

In the instant case, the claims are directed to a method of evaluating a compound for the ability to inhibit binding of an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1 wherein the proteins are biologically active fragments of the proteins. Thus, the claims encompass methods using variant proteins. Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active fragments, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the

specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible fragments of the subunits.

It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. As an example of the unpredictable effects of mutations on protein function, Mickle et al. (Mickle JE et al. Genotype-phenotype relationships in cystic fibrosis. Med Clin North Am. 2000 May;84(3):597-607) teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving ride to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (Voet et al. Biochemistry. 1990. John Wiley & Sons, Inc. pages 126-128 and 228-234) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in

associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. teaches that in certain cases, a change of only two-amino acid residues in a protein results in switching the binding of the protein from one receptor to another (Yan et al., Two-amino acid molecular switch in an epithelial morphogen that regulates binding to two distinct receptors. *Science* 290: 523-527, 2000). Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claims 45-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are drawn to a method of evaluating a compound for the ability to inhibit binding of an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1, wherein the proteins are biologically active fragments of the proteins Thus, the claims encompass methods using variant proteins. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. The specification and claim do not place any limit on the number of amino acid substitutions, deletions, insertions and/or additions that may be made to the proteins. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claims do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and

because the genus is highly variant one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 45-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Stephens et al. (1996).

The claims are drawn to a method of evaluating a compound for the ability to inhibit binding of an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1. The Stephens reference teaches that the coexpression of the rat Kvβ1 subunit with the mouse Kv1.1 K+ channel in Chinese hamster ovary cells caused an increase in the rate of inactivation of whole-cell current. Current decayed in a bi-exponential fashion with a fast voltage-dependent and a slower voltage-independent component. The claims are anticipated because the Stephens reference teaches a method of measuring the effect of a compound, peptides from the amino terminal protein of Kvβ1 on the binding of the an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1, see page 251, Figure 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (1996) in view of U.S. Patent No. 6,080,557 (Sims et al.).

The claims are drawn to a method of evaluating a compound for the ability to inhibit binding of an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1, wherein as candidate compound is added to a host cell, wherein the expression of a reporter gene is monitored. The Wang reference teaches that the interaction and functional properties of two alternatively spliced human Kvβ subunits, 1.2 and 1.3, with Kvβ subunits 1.1, 1.2, 1.4, and 1.5. In the yeast two-hybrid assay, they found that both Kvα subunits interact specifically through their conserved C-terminal domains with the N termini of each Kvβ

subunit. Thus, the Wang reference teaches a method of measuring the interaction between an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1, by measuring the expression of a reporter gene. The Wang reference does not teach the addition of a candidate compound. The '557 patent discloses the yeast two hybrid system was developed as a way to test whether two proteins associate or interact directly with each other and was then modified to serve as a method to "capture" candidate proteins that interact with a known protein of interest or "bait." The bait protein is expressed as a fusion protein with the DNA-binding domain of GAL4, a yeast transcription factor, in a specially designed yeast strain (Y190) containing reporter genes under GAL4 control (column 15, lines 30-39). The '557 patent further discloses that the functional interaction between proteins also permits screening for small molecules that interfere with the association (column 15, lines 63-65). Thus, it would have been obvious to one of skill in the art at the time the invention was made to practice a method of evaluating a compound for the ability to inhibit binding of an α-subunit intracellular receptor region of a voltage gated K channel to an amino-terminal inactivation region of a potassium channel protein, wherein the voltage gated channel proteins are Kv1.1 and Kvβ1, wherein as candidate compound is added to a host cell, wherein the expression of a reporter gene is monitored. The motivation is provided in the '557 patent which discloses that the yeast two hybrid method can be used for the screening of compounds (column 16, limes 5-20).

References

The Office will no longer be supplying paper copies of U.S. Patents cited in Office Actions. Applicant is advised that the cited U.S. patents and patent application publications are available for download via the Office's PAIR. As an alternate source, all U.S. patents and patent application publications are available on the USPTO web site (www.uspto.gov), from the Office of Public Records and from commercial sources. Applicant may direct inquiries about the use of the Office's PAIR system to the Electronic Business Center (EBC) at http://www.uspto.gov/ebc/index.html or 1-866-217-9197.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Murphy whose telephone number is (571) 272-0877. The examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Patent Examiner
Art Unit 1646
August 11, 2004

JOSEPH MURPHY
PATENT EXAMINER